REMARKS

Claims 19-27 are pending. No new matter has been added by way of the present amendments. For instance, claims 1-18 have been cancelled and new claims 19-27 have been added. New claims 19 and 23 are supported by originally filed claims 1, 7, 8, 10 and 12. New claims 20 and 21 are supported by originally filed claims 13 and 14, respectively. New claim 22 is supported by originally filed claim 9. New claim 24 is supported by originally filed claims 1, 7, 8, 10, 12 and 15. New claim 25 is supported by originally filed claim 16. Lastly, new claims 26 and 27 are supported by original filed claims 17 and 18. Accordingly, no new matter has been added.

In view of the following remarks, Applicant respectfully requests that the Examiner withdraw all outstanding rejections and allow the currently pending claims.

Issues under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1-14 under 35 U.S.C. § 112, second paragraph for the reasons recited at page 2 of the outstanding Office Action. Applicant respectfully traverses.

First, the Examiner asserts that claims 1-14 omit essential steps such as a step of inducing ciliary muscle contraction and evaluating the results. Applicant disagrees.

Claims 19-23 relate to an experimental model for evaluating the effect of a medicine against asthenopia. As such, although the model requires the contraction of the ciliary muscle, this is not technically a step. Rather, these claims relate to a

model in which ciliary muscle is in the state of asthenopia, thus making it possible to replicate *in vitro* the asthenopia which occurs *in vivo*. Also, there is no requirement for a step involving evaluation of results *per se*. Claims 19-23 relate to the experimental model, not to a method of evaluating any results that might be derived from the model. These claims recite repeatedly contracting ciliary muscle from a non-human animal *in vitro* with an inducer of smooth muscle contraction. This is the way in which the state of asthenopia is achieved in the ciliary muscle. This is not technically a step, but rather an operation carried out to create the model and is fully definite.

Method claims (for instance claims 24-27) are present, however, these claims specifically recite steps.

Second, the Examiner has rejected certain claims for reciting "substantially stable decrease." Applicant traverses and submits that the claims require the decrease to be 50 ± 30% in the tension of muscular contraction. This phrase is fully definite.

In summary, Applicant respectfully submits that the present claims fully satisfy the requirements of 35 U.S.C § 112, second paragraph. Reconsideration and withdrawal of these rejections are therefore requested.

Issues under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-8, 11, 12 and 15-18 as being anticipated by JP 07-133225 (hereinafter referred to as JP '225). Applicant respectfully traverses.

The Examiner, by referencing paragraphs 0022-0023 of JP '225, has alleged that JP '225 investigates compound A for effectiveness over contraction of ciliary muscle (CM). A review of paragraph 0022 of JP '225 reveals a discussion that "it pretreats by this invention compound A for 30 minutes before addition, and is KCl."

In other words, JP '225 discloses the treatment of CM with KCl, a CM contraction-inducing substance, after the treatment of CM with compound A, a contraction-inhibitor. Thus, JP '225 fails to suggest or disclose an experimental model comprising CM in a state of asthenopia which is prepared by preliminarily repeatedly contracting the CM to show a decrease of 50 ± 30% in the tension of muscular contraction. Further, JP '225 fails to suggest or disclose that the state of asthenopia is caused by repeatedly contracting the CM *in vitro* with an inducer of smooth muscle contraction comprising at least one inducer selected from a chemical stimulant, an electrical stimulant and combinations thereof. JP '225 also fails to suggest or disclose a method of preparing the present experimental model or a method of using the present experimental model. Accordingly, there is no anticipation based upon JP '225. Reconsideration and withdrawal of this rejection are therefore requested.

Applicant further points out that the experimentation described in paragraph 0022 of JP '225 is performed in accordance with the method described in *Exp. Eye Res.*, 53, 33-38 (1991), a copy of which is attached. Figure 3 of *Exp. Eye Res.*, 53, 33-38 (1991) shows as "ciliary muscle (CM)" the results of

force response of ciliary muscle during the contraction with acetylcholine and K^+, which are CM contraction-inducing substances. Figure 5 of the same reference shows as "ciliary muscle" the results of force response of ciliary muscle during the contraction with aceclidine and pilocarpine, which are CM contraction-inducing substances. According to the reported data the fatigue of CM is not generated as in the CM of the present invention. Thus, the method utilized by JP '225 (that disclosed in *Exp. Eye Res.*, 53, 33-38 (1991)) also fails to suggest or disclose the present claims.

In summary, there is no anticipation based upon the cited art, or based upon the methods referenced in the cited art. Reconsideration and withdrawal of this rejection are requested.

Issues under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-18 as being obvious over JP '225 in view of Kitagawa, Japanese Journal of Pharmacology, 1989, Vol. 49, supp. p.281 (hereinafter referred to as Kitagawa) and Yoshikawa, U.S. Patent No. 5,338,668 (hereinafter referred to as Yoshikawa '668). Applicant respectfully traverses.

JP '225 was discussed and distinguished above. Neither of the secondary references of Kitagawa or Yoshikawa '668 is able to cure the deficiencies of JP '225. Kitagawa discloses acetylcholine-induced contraction of smooth muscles. Yoshikawa discloses assessing the effects of drugs on smooth muscles before and after electrical stimulation. However, regardless of the disclosure of the secondary references, without the present

experimental model, method of preparation or method of use being disclosed by JP '225, there can be no *prima facie* case of obviousness.

That is, when all of the cited references are taken in combination, the Examiner has still failed to render obvious an experimental model wherein ciliary muscle from a non-human animal is placed in a state of asthenopia by repeatedly contracting said ciliary muscle *in vitro* with the recited inducer(s) of smooth muscle contraction until the ciliary muscle shows a decrease of 50 ± 30% in the tension of muscular contraction. The method of preparation and the method of use of the experimental model are likewise non-obvious.

Stated in other words, asthenopia is a symptom caused by the fatigue of the ciliary muscle generated by prolonged or intense use of the eyes. In this regard, please refer to the section of "eyestrain" in the enclosed Medical Dictionary, Second Edition, p.236, Oxford, NY, Oxford University Press (1998). Conventionally, an effective drug, other than perhaps chondroitin sulfate, has not been developed for asthenopia. The reason why other drugs have not been developed is that an effective experimental model exhibiting asthenopia has not been found, thus, the necessary evaluation of such drugs could not be performed. Thus, the types of induction disclosed in the secondary references is irrelevant since JP '225 fails to suggest or disclose an experimental model, method of preparation or method of use as currently claimed.

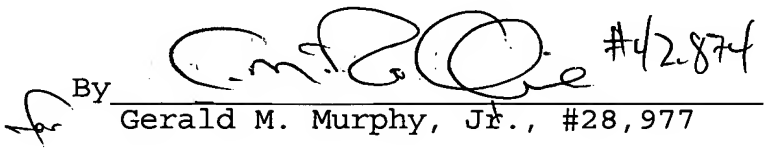
Accordingly, there exists no *prima facie* case of obviousness. Reconsideration and withdrawal of this rejection are respectfully requested.

If the Examiner has any questions or comments, please contact Craig A. McRobbie, Reg. No. 42,874, at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP



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Attachments: *Exp. Eye Res.*, 53, 33-38 (1991); and
Medical Dictionary, Second Edition, p.236, Oxford, NY, Oxford University Press (1998).

Exp. Eye Res. (1991) 53, 33–38

Differential Smooth Muscle-like Contractile Properties of Trabecular Meshwork and Ciliary Muscle

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The contractile properties of bovine trabecular meshwork and ciliary muscle strips were investigated using an electromagnetic force-length transducer for isometric force measurements. Acetylcholine, pilocarpine and aceclidine administration resulted in dose-dependent contractions of trabecular meshwork and ciliary muscle. Absolute forces were approximately 10 times larger in ciliary muscle than in trabecular meshwork. Maximal force evoked by aceclidine (5×10^{-6} M), when compared to the pilocarpine (5×10^{-6} M) response, was significantly higher in trabecular meshwork than in ciliary muscle. The results were $172{\cdot}5 \pm 12{\cdot}6\%$ ($n = 7$) and $138{\cdot}9 \pm 4{\cdot}0\%$ ($n = 8$, $P < 0{\cdot}05$), respectively. Depolarization induced by raised external potassium (120 mM), when compared to the acetylcholine response (10^{-3} M), resulted in a small contraction of $19{\cdot}3 \pm 4{\cdot}2\%$ in trabecular meshwork ($n = 5$), and of $59{\cdot}0 \pm 13{\cdot}7\%$ in ciliary muscle ($n = 4$, $P < 0{\cdot}01$). Both responses were inhibited by atropine (10^{-6} M).

The differential potassium effect may be explained by the large number of cholinergic nerve endings in ciliary muscle as compared to trabecular meshwork tissue. Recently, a dissociation between the effects of aceclidine on outflow resistance and accommodation has been described. Our data are consistent with these observations and provide evidence for a direct role of trabecular meshwork contractility in aqueous outflow regulation.

Key words: isolated trabecular meshwork; isolated ciliary muscle; bovine tissue; contractility; acetylcholine; pilocarpine; aceclidine; aqueous humour; outflow facility; smooth muscle; intraocular pressure; glaucoma.

1. Introduction

The mechanisms regulating aqueous humour outflow and intraocular pressure have been the subject of extensive investigation. In chronic simple glaucoma it is believed that the relation between aqueous humour production and outflow is disturbed by a decreased outflow facility (for review see Lütjen-Drecoll and Rohen, 1989). The main site of outflow resistance in the chamber-angle pathways is thought to be located in the juxtacanalicular trabecular meshwork (Bill and Svedbergh, 1972; Rohen, Futa and Lütjen-Drecoll, 1981; Mäepea and Bill, 1989). The mechanisms of outflow regulation by the trabecular meshwork (TM) is therefore of clinical importance.

A large number of drugs and their action on outflow facility have been investigated. These include cholinomimetics (Bárány, 1965), adrenergic agents (Neufeld and Sears, 1975), cytochalasins (Kaufman, 1987), chelators (Bill, Lütjen-Drecoll and Svedbergh, 1980), tryptic enzymes (Hamanaka and Bill, 1988), angiotensin and ergotamine (Kaufman and Rentzhog, 1981). All of these drugs would be capable of influencing structure and/or tone of smooth muscle tissue. Disinsertion of the ciliary muscle (CM) from the scleral spur has been established as a model for distinguishing between the role of CM in facility regulation and the influence of the meshwork in higher primates (Kaufman and Bárány, 1976).

Nevertheless, it is still unclear as to how TM or other chamber angle tissues influence outflow facility. TM cell cultures showed morphological (Tripathi and Tripathi, 1984) and electrophysiological (Coroneo et al., 1991) evidence for contractility and excitability. This suggested a smooth muscle-like function of meshwork tissue. Smooth muscle-specific contractile filaments have been found in TM cells (Iwamoto and Tamura, 1988; Coroneo et al., 1991; De Kater, Spurr-Michaud and Gipson, 1990). Recently, regions containing alpha-smooth muscle actin and myofibroblasts have been described in the bovine chamber angle (Flügel, Tamm and Lütjen-Drecoll, 1991). The aim of this study was to directly test the possible contractile properties of anterior chamber angle tissue.

2. Materials and Methods

Tissue Preparation

Bovine eyes were obtained from a local abattoir and transported on ice immediately to the laboratory. The eyes were bisected 10 mm behind the limbus. Vitreous and lens were cut away with fine scissors. The anterior chamber disc, including the whole ciliary body, was cut into equal quarters. With the corneal epithelial side downwards, the iris was retracted and the pectinate ligament carefully detached. With minimal retraction of the meshwork, the iris was totally excised

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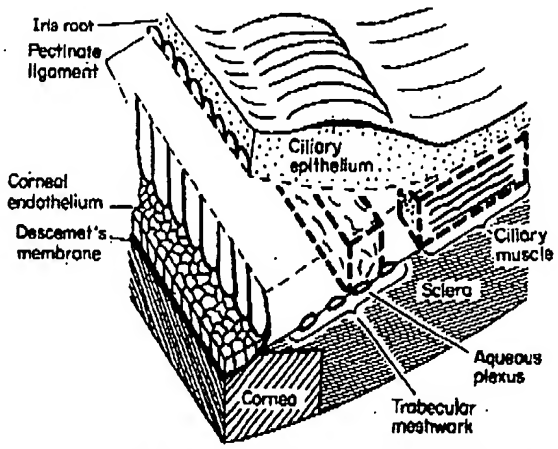

FIG. 1(A). Schematic drawing of the bovine chamber angle illustrating the preparation of strips from TM and CM. The pectinate ligament was detached and the ciliary epithelium and connective tissue were removed as indicated. Circular strips were obtained from the TM region adjacent to the aqueous plexus. (To increase contrast, the remaining TM region is left blank.) Meridional strips were prepared from the CM. Strip orientation is indicated by dotted lines.

by horizontal cuts. A schematic view of the tissue preparation is given in Fig. 1(A).

Trabecular Meshwork Strips

Only TM and CM tissue remained on the corneo-scleral segment, distinguishable by structure and pigmentation. Two vertical incisions were made in a circular direction, one in the black pigmented anterior meshwork, and the other 0·5 mm anterior to the CM insertion. Both circular cuts and the resulting strip were oriented parallel to the corneal insertion of the pectinate ligament. The tissue strip between these cuts was approximately 0·5 mm wide and 4 mm long and showed the typical velcro-like structure of TM. It was removed from the sclera with careful cuts as a circular strip.

Ciliary Muscle Strips

The CM is located posterior to the TM and distinguished by its deep pigmentation. Meridional strips were excised at a right angle to the circular ciliary body and treated as described above. Stretching of the tissue was carefully avoided in all preparations, and tissues were repeatedly rinsed with Hepes-buffered saline at 4°C to avoid damage by drying. The strips were placed in Hepes-buffered saline and connected to a force-length-transducer immediately after preparation.

Force-Length Transducer

To obtain isometric recordings of very small forces developed by extremely elastic tissue strips (such as TM preparations), we have developed a force-length-transducer system similar to that described by Brutsaert et al. (1988). A schematic view is given in Fig. 1(B). A coil was placed in a homogenous magnetic field. A lever was attached to the coil. At the free end of this lever, a fine needle was connected to the tissue strip such that shortening of the strip resulted in a small rotation of the lever-coil system. This rotation was measured by an optoelectronic device. The lever acted as a shutter between an infrared light-emitting diode and a photodiode. A second photodiode was used to subtract background light changes. The whole device was shielded by a black case. An electronic proportional-integral feedback circuit nullified the above mentioned small rotation by increasing the counteracting coil current with an adjustable raising time to avoid oscillations. This resulted in a 'position clamp' behaviour. The defined length of the tissue strips could be varied by changing the nominal value of the feedback-unit. Coil current was calibrated in Micronewton (μN). It was possible to measure forces from 0·5 μN to 2000 μN with resulting length-changes of the tissue strips of less than 10 μm. Rise time was 100 times shorter than the observed biological phenomena. The coil current was converted by an analog-digital converter, recorded simultaneously on floppy disc, and plotted on the screen by a microcomputer (Schneider CPC 6128, Türkheim, FRG).

Perfusion Chamber

The tissue-strips were mounted in a chamber with an acrylic glass water jacket maintained at 36°C. The chamber was continuously perfused with warmed Ringer's solution (see below) at a perfusion rate of 6 ml min^{-1}. The hydrodynamic form of the chamber allowed fast solution changes with minimal hydraulic disturbances of the tissue preparation. The exchange rate of the chamber's content was > 95% min^{-1} at a bath volume of 2 ml. Different solutions could be automatically selected by the same microcomputer which recorded the digitalized data by controlling electromagnetic valves between a roller-pump and the solution's reservoirs.

Solutions

Modified Ringer's solution of the following ionic concentrations was used (mM): Na^+, 151; K^+, 5; Ca^{2+}, 1·7; Mg^{2+}, 0·9; Cl^-, 131; SO_4^{2-}, 0·9; $H_2PO_4^-$, 1; HCO_3^-, 28. In solutions containing 120 mM potassium an equivalent amount of Na^+ was replaced by K^+. All solutions contained 5 mM glucose and were gassed with 5% CO_2 in air, resulting in a pH of 7·4.

Drugs

The following drugs were dissolved in the perfusate: aceclidine (Chibret, Munich, FRG), acetylcholine,

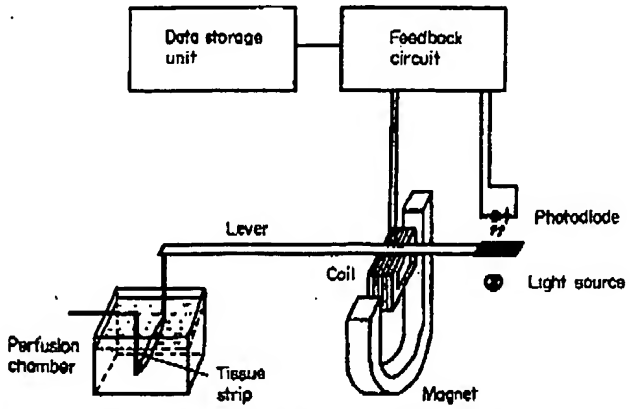

FIG. 1(B). The tissue strip was mounted in a perfusion chamber and connected to the force-length-transducer. Shortening of the strip resulted in a small rotation of the lever-coil system in a magnetic field. This rotation was measured by a photodiode and nullified by the counteracting coil-current, which was calibrated in micronewton (μN).

atropine, and pilocarpine (Sigma, Deisenhofen, FRG). In the case of acetylcholine, no cholinesterase-inhibitors were added because of the permanent rapid perfusion of the perfusion chamber.

Force Measurements

Resting tension was adjusted to obtain maximal response using an acetylcholine pulse of 3 min duration. After attachment of the strips to the transducer, the strips were allowed to rest under control conditions. Only strips with a stable tone were used for further measurements. All force measurements were performed isometrically. Due to the complex structure of the TM and the small variations in preparing the tissue strips it was impossible to correlate the force measurements to geometrical parameters, weight or volume of the strips. Therefore, unless otherwise indicated, all force measurements are given as relative values in comparison with the acetylcholine (or pilocarpine) response.

Calculations

As we obtained the eyes from a large pool, the preparation of two eyes from the same animal was unlikely. Mostly 2–3 strips were prepared from one eye. Mean values were calculated from the different measurements for each eye. The number of experiments indicated in this work represent numbers of values obtained from different eyes. Statistical analysis was done using Student's *t*-test.

3. Results

Acetylcholine Response

Figure 2 shows a typical recording of force development by a TM strip. Superfusion by an acetylcholine-containing solution resulted in an immediate, steep force development, reaching a maximum after 1 min. With constant administration of the drug a stable tone developed, sometimes after a phasic force peak. This behaviour could be observed with all the stimulating drugs used. After changing to a drug-free Ringer's solution, the tone decreased to the basal level within 2 min. As demonstrated in Figs 3(A) and (B), acetylcholine resulted in a dose-dependent contraction of TM and CM strips. The maximal response was reached at 10^{-5} M; 10^{-7} M acetylcholine had no effect (data not shown).

The response to 10^{-6} M (Fig. 2) and 10^{-5} M (Fig. 3) acetylcholine could be completely blocked by 10^{-5} M atropine. Recovery of contractions evoked by cholinergic agents following atropine wash-out, was very slow and incomplete after 60 min (not shown). The force peaks were reproducible and repeated stimulation evoked no measurable fatigue. Spontaneous activity could not be observed in either tissue.

Response to Depolarization Induced by Raised Extracellular Potassium Concentration

Elevation of the extracellular potassium concentration (120 mM K^+) resulted in a reproducible

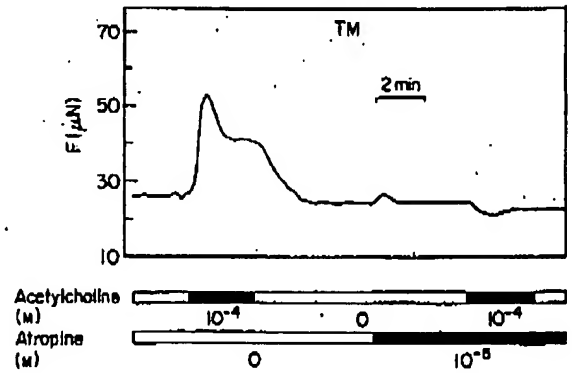

FIG. 2. Isometric force development by a TM strip. Administration of 10^{-6} M acetylcholine resulted in a phasic-tonic force response. This was completely inhibitable by atropine (10^{-5} M).

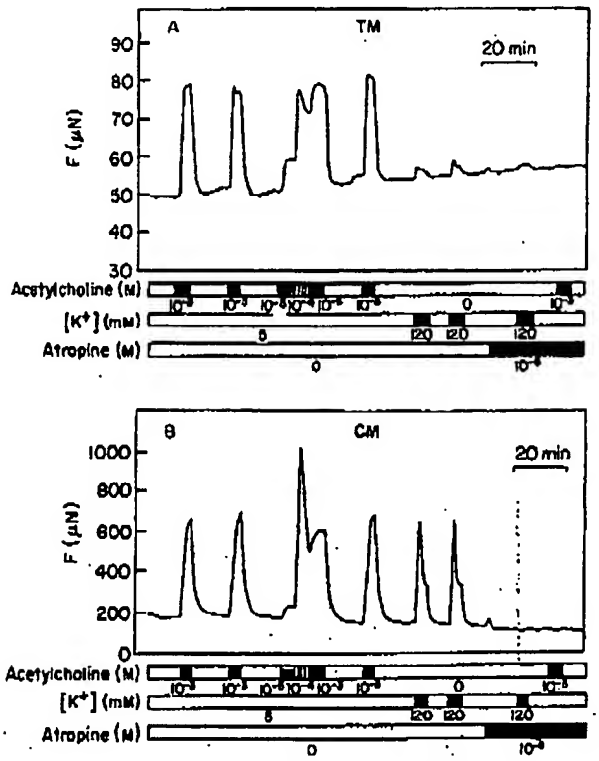

FIG. 3. Force response of TM (A) and CM (B) to raised extracellular [K+] (right side). When compared to the acetylcholine response, [K+]-elevation showed a similar effect in CM, but nearly no effect in TM. The contractions were completely inhibited in CM and reduced in TM by atropine. The acetylcholine response (left side) was reproducible and dose-dependent.

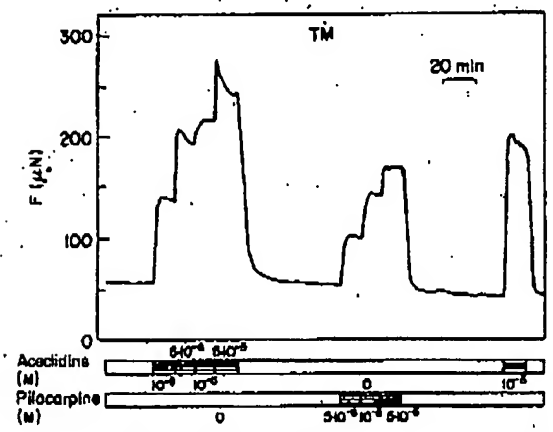

FIG. 4. Original recording of force development by a TM strip. Aceclidine and pilocarpine administration resulted in reproducible dose-dependent contractions.

biphasic contractile response in both tissue types. The relative tension evoked by 120 mM K^+, compared to the acetylcholine response, was approximately 3 × higher in CM than in TM strips. Figures 3(A) and (B) show typical original recordings of 120 mM K^+- and acetylcholine- evoked contractions in TM and CM. The

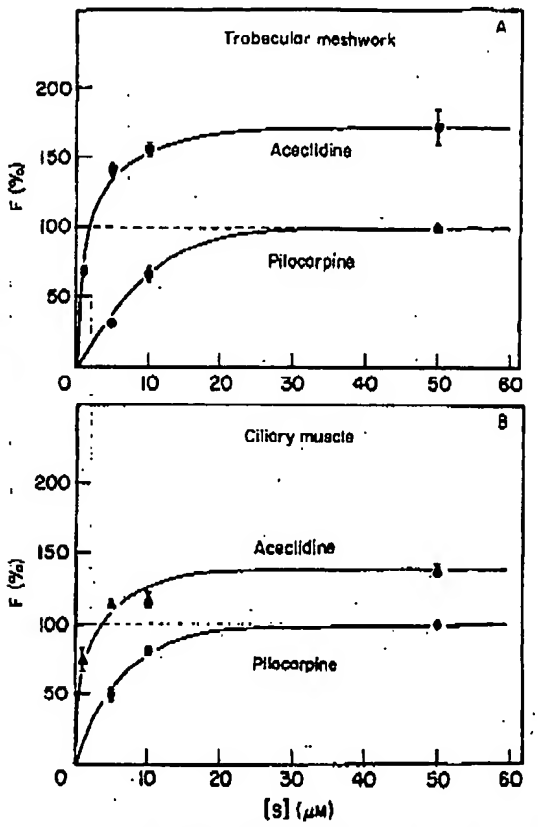

FIG. 5. Summary of 17 (CM) and 16 (TM) experiments as shown in Fig. 4. Values are given as percentage of the maximal pilocarpine response. The symbols represent mean values ± s.e.m. Maximal force evoked by aceclidine administration was 172·5 ± 12·6% ($n = 7$) with TM and 138·9 ± 4·0% ($n = 8$) with CM strips ($P < 0.05$).

relative force developed in an elevated K^+-solution was 59·0 ± 13·7% ($n = 4$) in CM and, only, 19·3 ± 4·2% ($n = 5$) in TM, when related to the acetylcholine response ($P < 0.01$).

Following perfusion with an atropine-containing solution (10^{-5} M) for 5 mins, the contractile response to an external K^+ concentration of 120 mM was completely abolished in CM and markedly reduced in TM. This demonstrates the neurogenic origin of the depolarization-response.

Effects of Pilocarpine and Aceclidine

Figure 4 demonstrates the dose-dependent contractions of TM in response to pilocarpine and aceclidine. This could be completely inhibited by atropine (10^{-6} M, not shown). The dose-response relation and the maximal response, however, were significantly different between TM and CM.

Figure 5 summarizes the data obtained from 33 recordings. The maximal contraction evoked by aceclidine in TM was 172·5 ± 12·6% ($n = 7$) and in CM 138·9 ± 4·0% ($n = 8$, $P < 0.05$).

We analysed the data by linear transformation

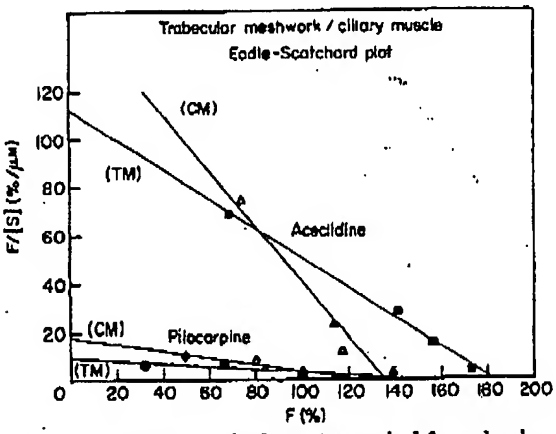

FIG. 6. Aceclidine- and pilocarpine-evoked force development shown as an Eadie-Scatchard plot. Assuming a linear correlation between receptor occupancy and isometric force development, F_{max} (aceclidine) was calculated 181·3% (TM) and 135·0% (CM), ED_{50} $1·6 \times 10^{-6}$ M (TM) and $8·6 \times 10^{-7}$ M (CM), respectively.

employing the method of Eadie-Scatchard (Fig. 6). With [S] representing the concentration of aceclidine and pilocarpine, respectively, F/[S] was plotted against F. Apparent F_{max} (the maximal force induced by aceclidine, which can be directly seen as the point of intercept with the bottom line) was 181·3% for TM and 135·0% for CM. ED_{50} (aceclidine dosage eliciting half-maximal force response) was calculated $1·6 \times 10^{-6}$ M (TM) and $8·6 \times 10^{-7}$ M (CM), respectively.

4. Discussion

This is the first study which directly demonstrates contractile properties of the trabecular meshwork. The contractile properties of TM in bovine eyes are different from those of CM, when observing the effect of elevated K^+-concentration and acetylcholine, pilocarpine and aceclidine administration.

Recently, we have been able to demonstrate action potentials in bovine TM cells which were not inhibitable by tetrodotoxin (Coroneo et al., 1991). This is a typical behaviour of smooth muscle cell membranes. Therefore, it is tempting to speculate that contractions of the TM, itself, would influence outflow regulation in the bovine eye.

Due to the anatomical proximity of both tissues in the eye of higher primates, it is conceivable that contractions of TM could be related to CM insertion into the TM. In the bovine eye, however, the ciliary muscle is rudimentary and posteriorly located (Rohen, 1964; Tripathi, 1974; Flügel et al., 1991). In the present study, both tissues could be prepared separately, and were easily distinguishable by structure and colour. Furthermore, the meshwork region adjacent to the CM was not used for the measurements. Finally, CM contamination of the TM preparations alone cannot explain the different contractile responses of both tissues to several agents observed in the present study.

Recently, the bovine chamber angle has been examined ultrastructurally and immunocytochemically. Myofibroblasts, containing α-smooth muscle actin, have been found between CM and the reticular meshwork region (Flügel et al., 1991). These cells are likely to be responsible for the contractile activity of TM preparations used in the present study.

In the CM, a large number of cholinergic nerve terminals have been described (Ishikawa, 1962; Ruskell, 1982). TM, however, contains markedly fewer nerve endings (Rohen, 1964; Ruskell, 1982). In the present study atropine reduced the contractile response of the TM and inhibited completely the response of the CM to depolarization. Consequently, the main part of force development must be due to a depolarization-induced acetylcholine release from cholinergic nerve terminals rather than a result of depolarization of the muscle cell membrane per se. This phenomenon has already been found in CM tissue from cow, dog and man where atropine and tetrodotoxin inhibited depolarization-induced contractions (Suzuki, 1983; Ito and Yoshitomi, 1986; Lograno and Reibaldi, 1986).

In contrast to the CM, depolarization mediated by a raised external potassium concentration resulted in a consistently smaller contractile response of TM. This effect would be predicted from the different density of cholinergic nerve terminals in these tissues. The small atropine-resistant component of TM force development might be due to the release of non-muscarinic transmitters and/or a direct depolarization-effect in these cells.

Clinical observation shows that aceclidine is more effective in lowering intraocular pressure and has less effect on accommodation than pilocarpine in humans (Keren and Treister, 1980). Recent experimental data support these observations using primate eyes (Erikson-Lamy et al., 1990). While these differences in primate eyes were thought to be related to different regions of the CM, we were able to show a significant difference of the aceclidine-induced contractions between bovine TM and CM. When related to the maximal pilocarpine action, aceclidine was more effective in eliciting contractions in TM than in CM strips. Thus, an influence on outflow facility by traction of chamber angle tissues outside the CM could be the mechanism of aceclidine action and could explain the difference between both cholinomimetics.

The biomechanical significance of TM contractility is not yet clear. TM contractions could narrow the spaces through which the aqueous humour flows and, therefore, result in a facility decrease. Alternatively, hydrodynamic behaviour of the juxtacanalicular tissue layer could be directly influenced by TM traction, as occurs with CM traction. In both cases, there would be a complex interaction of CM and TM contractile structures. We have begun further studies to evaluate

the significance of TM contractility in outflow regulation.

Acknowledgements

The skilful technical assistance of Astrid Krolik and Marianne Koch is gratefully acknowledged. This work was supported by grant DFG Wi 328/11.

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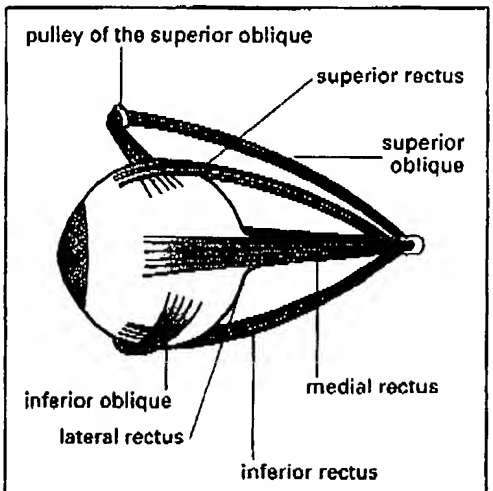

Extrinsic muscles of the eye

eyebrow *n.* the small fringe of hair on the bony ridge just above the eye. It helps to prevent moisture from running into the eye. Anatomical name: **supercilium**.

eyeground *n.* the inside of the eye as seen through an ophthalmoscope; the ocular fundus.

eyelash *n.* one of the long stiff hairs that form a row projecting outwards from the front edge of the upper and lower eyelids. The eyelashes help keep dust away from the eye. Anatomical name: **cilium**.

eyelid *n.* the protective covering of the eye. Each eye has two eyelids consisting of skin, muscle, connective tissue (**tarsus**), and sebaceous glands (**meibomian** or **tarsal glands**). Each eyelid is lined with membrane (*conjunctiva) and fringed with eyelashes. Stimulation of the pain receptors in the cornea causes the eyelids to close in a reflex action. Inflammation of a meibomian gland can result in a *chalazion. Anatomical names: **blepharon**, **palpebra**.

eyepiece *n.* the lens or system of lenses of an optical instrument, such as a microscope, that is nearest to the eye of the examiner. It usually produces a magnified image of the previous image formed by the instrument. *Compare* OBJECTIVE.

eyespot *n.* a small light-sensitive area of pigment found in some protozoans and other lower organisms.

eyestrain *n.* a sense of fatigue brought on by use of the eyes for prolonged close work or in persons who have an uncorrected error of *refraction or an imbalance of the muscles that move the eyes. Symptoms are usually aching or burning of the eyes, accompanied by headache and even general fatigue if the eyes are not rested. Medical name: **asthenopia**.